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EXAMINER

KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
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1636

11

DATE MAILED: 08/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

09/868,663

TMSIT ET AL.

Examiner

Sumesh. Kaushal Ph.D.

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 13 May 2003.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-16 is/are pending in the application.

4a) Of the above claim(s) 6 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-16 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-692)

4) Interview Summary (PTO-413) Paper No(s). _____

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

5) Notice of Informal Patent Application (PTO-152)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____

6) Other: _____

DETAILED ACTION

Applicant's response filed on 05/13/03 has been acknowledged.

Claims 2-16 are amended.

Claims 1-16 are pending and are examined in this office action.

► *Applicants are advised to follow Amendment Practice under revised 37 CFR §1.121 (<http://www.uspto.gov/web/offices/pac/dapp/ropa/preognotice/revamdtprac.htm>). Each amendment document that includes a change to an existing claim, or submission of a new claim, must include a complete listing of all claims in the application. After each claim number, the status must be indicated in a parenthetical expression, and the text of each claim under examination (with markings to show current changes) must be presented. The listing will serve to replace all prior versions of the claims in the application.*

Election/Restrictions

Applicant's election without traverse of species Growth factors and Epithelial cells in Paper No. 10 is acknowledged.

To correct the error in the restriction election mailed on 11/13/02 regarding the election of species, the Endothelial cells has been joined with cerebral cells and Epithelial cells has been joined with retinal cells. Elected species Epithelial cells (retinal cells) has been examined in this office action.

Claim Objections

Claim 5 and 6 are objected to because of the following informalities: The instant claims encompasses non-elected subject matter "endothelial cells and cerebral cells". Appropriate correction is required.

Claims 10-16 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim *cannot depend from any other multiple dependent claim*. See MPEP § 608.01(n). Accordingly, the claims has are not been further treated on the merits.

Specification

The disclosure is objected to because of the following informalities: The specification refers to Fig 1, Fig 2 and Fig 3 on page 18. However no figures were filed with the instant specification. In addition the application does not contain an abstract.

Appropriate correction is required

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-7 and 10-16 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by Greenwood et al (US 6,183,735 2001).

Greenwood teaches an injectable, stable, immortalized, non-tumorigenic rat retinal pigment epithelial cell line (RPE: IO/LD/7), wherein the cells of the cell line comprise a polynucleotide comprising a heat-sensitive SV40 tsa58 T-antigen oncogene. The cited art further teaches that these RPE cells can be non-tumorigenically integrated into the retina of a mammalian host. The RPE cell line further comprises an expression vector comprising a polynucleotide coding for a polypeptide for treating ophthalmological or neurological disorders. The cited art further teaches that these RPE cells can be integrate non-tumorigenically into the retina of the mammalian host to produce the polypeptide in the eye (see col. 11 example-3, col.12 example-4; col.15-16). The cited art further teaches an in-vivo injectable preparation of cells which contains 2.10×10^4 cell/ μ l (col.12, line 56-59). In addition the cited art teaches the making of cell suspension for Flux-cytometry using the collagenase/dispase treatment of cells to make single cell suspension suspended in EDTA, which prevent the aggregation of suspended cells (col.7 lines 5-36). The cited art also teaches the treatment of RPC cells with trypsin to make cells suspension (col.11, lines 6-24). Besides the biochemical treatment the process of trypsinization inherently encompasses a physical treatment of cells (to make single cell suspension), which requires shaking of repeated pipetting of displaced cells. Furthermore a cell suspension used for Flux-cytometry is an aggregate free preparation that inherently comprises a single cell suspension of RPE cells, which is well below the size range of 30-200 microns. Thus the cited art clearly anticipate the invention as claimed.

Claims 1-7 and 10-16 are rejected under 35 U.S.C. 102 (b) as being anticipated by Greenwood et al (WO 97/40139, 1997).

Even though the WO 97/40139, 1997 is document in French language the disclosure is identical to the US 6,183,735, since the US '735 patent is national stage application (371) of WO 97/40139, 1997 (PCT/FR97/00709). Accordingly the WO97/40139 clearly teaches an injectable, stable, immortalized, non-tumorigenic rat retinal pigment epithelial cell line (RPE: IO/LD/7), wherein the cells of the cell line comprise a polynucleotide comprising a heat-sensitive SV40 tsa58 T-antigen oncogene. The cited art further teaches that these RPE cells can be non-tumorigenically integrated into the retina of a mammalian host. The RPE cell line further comprises an expression vector comprising a polynucleotide coding for a polypeptide for treating ophthalmological or neurological disorders. The cited art further teaches that these RPE cells can be integrate non-tumorigenically into the retina of the mammalian host to produce the polypeptide in the eye (see page 17 example-3; page 19 example-4; page 28-29). The cited art further teaches an in-vivo injectable preparation of cells, which contains 2.10×10^4 cell/ μ l (page 20, line 10). In addition the cited art teaches the making of cell suspension for Flux-cytometry using the collaegenase/dispase treatment of cells to make single cell suspension suspended in EDTA, which prevent the aggregation of suspended cells (page 10, lines 15-26). The cited art also teaches the treatment of RPC cells with trypsin to make cells suspension (page 17, lines 5-19). Besides the biochemical treatment the process of trypsinization inherently encompasses a physical treatment of cells (to make single cell suspension), which requires shaking of repeated pipetteting of displaced cells. Furthermore a cell suspension used for Flux-cytometry is an

aggregate free preparation that inherently comprises a single cell suspension of RPE cells, which is well below the size range of 30-200 microns. Thus the cited art clearly anticipate the invention as claimed.

Claims 1-7 and 10-16 are rejected under 35 U.S.C. 102 (e) as being anticipated by Greenwood et al (US 6,090,624 2000).

Greenwood teaches an immortalized non-tumorigenic human retinal pigmentary epithelial cell line (RPC), wherein the cells of the cell line comprise a nucleic acid, which encodes a non-thermosensitive viral or cellular oncogene. The cited art further teaches that RPE cells when injected in-vivo integrate into the host retina (col.9 example-2; col.13 example-4, col.16 example-5). In addition the cited art teaches the making of cell suspension for Flux-cytometry using the collaegenase/dispase treatment of cells to make single cell suspension suspended in EDTA, which prevent the aggregation of suspended cells (col.8 lines 34-47). The cited art also teaches the treatment of RPC cells with trypsin to make cells suspension (col.12, lines 15-35). Besides the biochemical treatment the process of trypsinization inherently encompasses a physical treatment of cells (to make single cell suspension), which requires shaking of repeated pipetteting of displaced cells. Furthermore a cell suspension used for Flux-cytometry is an aggregate free preparation, which inherently comprises a single cell suspension of RPE cells, which is well below the size range of 30-200 microns. Thus the cited art clearly anticipate the invention as claimed.

Note: The invention as claimed encompasses a product by process wherein the product obtained by the process is indistinguishable from the product obtained in the cited art. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps (see MPEP §2113). Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). Given the broadest reasonable interpretation in the instant case, an injectable, immortalized, non-tumorigenic RPC preparation as taught by the prior art of record is indistinguishable from the invention as claimed. Furthermore, preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. *See In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). In addition, if the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. *See In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). Thus the cited art (Greenwood’s US 6,183,735; 6090624 and WO 97/40139) clearly anticipate the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Greenwood's US 6,183,735; 6090624 and WO 97/40139 as applied to claims 1, 3-6, 10-11 and 13-16 above, and further in view of Roux et al (J cell. Physiol.159:101-113, 1994).

As stated above Greenwood teaches an injectable, stable, immortalized, non-tumorigenic rat retinal pigment epithelial cell line (RPE: IO/LD/7), wherein the cells of the cell line comprise a polynucleotide comprising a heat-sensitive SV40 tsa58 T-antigen oncogene. The cited art further teaches that these RPE cells can be non-tumorigenically integrated into the retina of a mammalian host. The RPE cell line further comprises an expression vector comprising a polynucleotide coding for a polypeptide for treating ophthalmological or neurological disorders. The cited art further teaches that these RPE cells can be integrate non-tumorigenically into the retina of the mammalian host to produce the polypeptide in the eye (see col. 11 example-3, col.12 example-4; col.15-16). The cited art further teaches an in-vivo injectable preparation of cells which contains 2.10×10^4 cell/ μ l (col.12, line 56-59). In addition the cited art teaches the making of cell suspension for Flux-cytometry using the collaegenase/dispase treatment of cells to make single cell suspension suspended in EDTA, which prevent the aggregation of suspended cells (col.7 lines 5-36). The cited art also teaches the treatment of RPC cells with trypsin to make

cells suspension (col.11, lines 6-24). Besides the biochemical treatment the process of trypsinization inherently encompasses a physical treatment of cells (to make single cell suspension), which requires shaking of repeated pipetting of displaced cells. Furthermore a cell suspension used for Flux-cytometry is an aggregate free preparation that inherently comprises a single cell suspension of RPE cells, which is well below the size range of 30-200 microns. However Greenwood does not teach the physical treatment of cells to prevent aggregate formation by filtration or screening and a cell preparation that comprises no aggregates of size greater than 30-200 microns.

Roux teaches a method of making cells suspension of adherent micro-vascular endothelial cells (page 102, col.1). The cited art teaches that after enzymatic treatment the brain tissue was suspended in 25 ml medium containing 25% BSA. The cells were centrifuged at 1000g for 10 minutes to eliminate contaminating cells and debris, passed through a 120 micron nylon mesh and incubated in medium containing collagenase/dispase. The clumps of cells were then layered over Percoll gradients prepared by centrifuging 50% isotonic Percoll at 25,000g for 1 hr. The band containing the isolated cells was removed for further use (page 102, cil.1 para.2). Roux clearly teaches a method of making single cell preparation, wherein the preparation contains no cells aggregates greater than 120 microns. Furthermore, Percoll gradients centrifugation results in isolation of cells in a single cell suspension.

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the preparation of cells as taught by Greenwood with the cell separation procedure as taught by Roux. One would have been motivated to make an aggregate free cell preparation, since such a preparation can be used to isolate individual colonies originated from a single cell.

One would have been further motivated to obtain individual clones, since each clone is a possible candidate that elicits unique cell characteristics especially after transformation. (see Greenwood's US 6,090,624 col.12, lines 36-43; US 6,183,735 col.11, lines 25-32). One would have a reasonable expectation of success, since the method of cell separation is routine in the art. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature Of Invention:

Invention relates to a pharmaceutical composition of genetically engineered mammalian epithelial cell used in a method for gene therapy.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of invention as claimed encompasses a pharmaceutical composition to be administered systemically comprising a genetically engineered mammalian epithelial cell that

produces any and all growth factors to treat any and all diseases of the nervous system. However, the specification only disclosed a genetically engineered immortalized mammalian cerebral endothelial cell line (RBE4) see page 18 line 17. The specification further teaches genetically engineered RBE4 cells are further modified to express β-galactosidase (RBEZ) or green fluorescent protein (RBE4/GFP) see pages 18 and 19. The specification further teaches that the injection of RBEZ (a cerebral endothelial cell line) into carotid artery results in the incorporation of injected cells in the lumen of intra-cerebral vessels and intra-parenchymatous extraluminal tissue (spec. page 26, lines 10-22, f-g-3). The specification as filed fails to disclose any genetically engineered non-tumorigenic, immortalized epithelial cells that can be used as pharmaceutical composition to treat any and all diseases of nervous system. The specification even fails to establish any nexus between a growth factor of interest (any and all) to particular disease of nervous system (Parkinson's disease, Alzheimer's disease, Huntington's disease, Neuropathy or Epilepsy etc).

State Of Art And Predictability:

The Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. (Rosenberg et al, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, Touchette, Nat. Med. 2(1) 7-8, 1996). None of the human studies to date has shown definite efficacy, despite more than 300 protocols involving 3000 patients since September 1990 (Anderson page 25 col.1 para.1). Most studies have neglected to include well-defined biochemical or clinical end

points that would clearly indicate whether the therapy is having a desired effect. For example, in original clinical trial to treat adenosine deaminase (ADA) deficiency, patients received a total of 11 infusions of genetically modified autologous T-lymphocytes along with polyethylene glycol (PEG)-ADA. After 7 years of therapy no definitive conclusion is drawn as to the contribution of gene therapy to the present state of health of patients (Touchette, page 7 col.3, para.1; Anderson page 29 col.1, para.6). Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success (Touchette page 7, col.1 para. 2; page 8, col.2 para 1-4). The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease. (Touchette, page 7, col.3, para.3). In instant case the brain is the both most genetically complex organ in the body and most difficult to treat. The cells in brain express more than 75,000 human genes than any other tissue in body, producing the greatest number of transcripts (Matthew et al Mol. Med. Today 11:485-93, 1998). Furthermore, the treatment of CNS in itself is unique since it include the post-mitotic neurons, heterogeneity of cell types, critical functions of specific neuronal circuits, limited access, volumetric constraints, and presence of the blood-brain barrier the challenges not usually at issue in peripheral gene therapy. In addition, the gene therapy for neurological disorders is currently an experimental concept that requires elucidation of physiological mechanisms and genetic basis underlying each neurological disease (Costantini et al Gene therapy 7:93-119, 2000, see pages 98-103). Even though, the gene therapy holds much promise to come, the success will only be achieved through continued rigorous research on the

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most fundamental mechanisms that contribute to a genetic disease along with the pathogenesis of the disease, gene delivery and gene expression in animals.

Furthermore, the word "Pharmaceutical" means the administration of a medicinal drug of therapeutic value, which has a characteristic interaction in a body, in terms of its absorption, distribution, metabolism and excretion (see Pharmaceutical and related terms in Merriam Webster's Dictionary). The current invention is drawn to a pharmaceutical formulation comprising genetically modified epithelial cells expressing any and all growth factor gene products, wherein the growth factor encodes a gene product to treat or prevent any and all diseases of nervous system in-vivo. The specification fails to provide any guidelines for determining which individual (with specific CNS disease) need to be administered with what pharmaceutical composition (cells expressing a specific growth factor). Furthermore, considering the scope of a disease of nervous system, the specification fails to provide any guidance regarding whether the disease would be the result of the loss of gene product or is the result of altered gene product function. It is even unclear whether the treatment of the disease associated with the gene product (as claimed) would require increase or decrease in the expression of the gene product.

Quantity Of Experimentation Required:

In instant case gene based therapies to treat any and all neuronal disorders by implanting genetically engineered epithelial cell from any and al origin which express any growth factor are not considered routine in the art and without sufficient guidance to a specific therapeutic gene the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the

unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Furthermore, it is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), *Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In instant case the considering applicant's limited disclosure and the state of art one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "**said patent**" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claim is indefinite because it is unclear what is “a nucleic acid sequence expressing an agent preventing aggregate formation or inhibiting the expression of an agent preventing the formation of aggregates” in this context.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
PATENT EXAMINER

Sumesh Kaushal
SUMESH KAUSHAL
PATENT EXAMINER